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(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).

(72) Inventors: NIELSEN, Jens, Høiriis; J.E. Ohlsensgade 14,4 tv., DK-2100 Copenhagen Ø (DK). FRIEDRICHSEN, Birgitte, Nissen; Agertoften 12, DK-2820 Gentofte (DK). RUGH, Susanne; Vandkarsevej 9, DK-2880 Bagsværd (DK). TROMHOLT, Niels; Christiansvej 26, DK-2920 Charlottenlund (DK). BJØRN, Søren; Marie Gubbes Allé 47, DK-2800 Lyngby (DK). KNUDSEN, Liselotte, Bjerre; Valby Langgade 49A, 1.Tv., DK-2500 Valby (DK). STURIS, Jeppe; Aakandevej 60, DK-3500 Vaerloese (DK).

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(57) Abstract

The present invention relates to a method for increasing the number and/or the size of beta cells, for stimulating beta cell proliferation and for preventing diabetes. The invention is based on the recognition that GLP-1 acts as a beta cell growth factor. The invention also relates to a method for preventing or curing Type I or Type II diabetes, a method for obtaining a less severe disease stage in a subject suffering from Type II diabetes as well as methods of delaying the progression of impaired glucose tolerance (IGT) or non-insulin requiring Type II diabetes to insulin requiring Type II diabetes. The invention also relates to a cure for diabetes.

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USE OF GLP-1 AND ANALOGUES FOR PREVENTING TYPE II DIABETES

The present invention relates to a method for increasing the number and/or the size of beta cells, for stimulating beta cell proliferation and for preventing diabetes. The invention is based on the recognition that GLP-1 acts as a beta cell growth factor. The invention also relates to a method for preventing or curing Type I or Type II diabetes, a method for obtaining a less severe disease stage in a subject suffering from Type II diabetes as well as methods of delaying the progression of impaired glucose tolerance (IGT) or non-insulin requiring Type II diabetes to insulin requiring Type II diabetes. The invention also relates to a cure for diabetes.

Diabetes is characterized by insufficiency of the pancreatic beta cells to maintain normoglycemia. In type 1 diabetes (IDDM) this is due to destruction of the beta cells by an autoimmune process whereas in type 2 diabetes (NIDDM) it is due to a combination of beta cell deficiency and peripheral insulin resistance. Under normal conditions the number of beta cells shows a positive correlation with the body mass. However in diabetic patients the number of beta cells is reduced and it is therefore pertinent not only to improve the function of the beta cells by therapeutical means but also to increase the number of beta cells. GLP-1 has been shown to stimulate glucose-induced insulin release and insulin biosynthesis and to restore glucose competence, but to our knowledge no reports on stimulation of beta cell proliferation have appeared. In our efforts to identify beta cell growth factors we discovered that GLP-1 indeed could stimulate beta cell proliferation in vitro. The proliferation was measured as incorporation of the thymidine analogue 5-bromo-2-deoxyuridine into DNA in insulin positive cells in pancreatic islet cells from newborn rats. GLP-1 was found to increase the number of labelled beta cells. This may have important implication for the treatment and/or prevention of diabetes.

Accordingly, the present invention relates to a method for increasing the number and/or the size of beta cells in a subject comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to said subject; a method for increasing the number of beta cells in a subject comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to said subject; a method for increasing the size of

beta cells in a subject comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to said subject; a method for stimulating beta cell proliferation in a subject comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to said subject; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist as a beta cell growth factor; a method for preventing Type I or Type II diabetes comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to a subject in need thereof; a method for increasing c-peptide levels in a subject comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to said subject; a method for obtaining a less severe disease stage in a subject suffering from Type II diabetes comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to said subject; a method for increasing the insulin synthesis capability of a subject comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to said subject; a method of delaying the progression of impaired glucose tolerance (IGT) to insulin requiring Type II diabetes comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to a subject suffering from IGT; a method of delaying the progression of non-insulin requiring Type II diabetes to insulin requiring Type II diabetes comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to a subject suffering from Type II diabetes; a method for curing Type I or Type II diabetes comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to a subject suffering from one of these diseases; a method according to any of the above methods which further comprises administering human growth hormone, a growth hormone releasing agent or a growth factor such as prolactin or placental lactogen to said subject; a method for increasing the number and/or the size of beta cells in a subject comprising administering human growth hormone, a growth hormone releasing agent or a growth factor such as prolactin or placental lactogen to said subject; and a method for stimulating beta cell proliferation in a subject comprising administering human growth hormone, a growth hormone releasing agent or a growth factor such as prolactin or placental lactogen to said subject.

The subject is preferably a mammal, more preferably a human.

The invention furthermore relates to the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for increasing the number and/or the size of beta cells in a subject; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for increasing the number of beta cells in a subject; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for increasing the size of beta cells in a subject; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for stimulating beta cell proliferation in a subject; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for treating a subject in need of a beta cell growth factor; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for preventing Type I or Type II diabetes; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for increasing c-peptide levels in a subject; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for obtaining a less severe disease stage in a subject suffering from Type II diabetes; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for delaying the progression of impaired glucose tolerance (IGT) to insulin requiring Type II diabetes; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for delaying the progression of non-insulin requiring Type II diabetes to insulin requiring Type II diabetes; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for increasing the insulin synthesis capability of a subject; the use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for curing Type I or Type II diabetes; a use according any of the above uses in a regimen which additionally comprises treatment with human growth hormone, a growth hormone releasing agent or a growth factor such as prolactin or placental lactogen; the use of human growth hormone, a growth hormone releasing agent or a growth factor such as prolactin or placental lactogen for the preparation of a medicament for increasing the number and/or the size of beta cells in a subject; the use

of human growth hormone, a growth hormone releasing agent or a growth factor such as prolactin or placental lactogen for the preparation of a medicament for stimulating beta cell proliferation in a subject.

In the present context "GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist" is also intended to comprise active metabolites and prodrugs of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist. A "metabolite" is an active derivative of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist produced when the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is metabolized. A "prodrug" is a compound which is either metabolized to GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist or is metabolized to the same metabolite(s) as GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist.

In the present context "GLP-1 agonists" is intended to indicate a molecule, preferably a non-peptide, which binds to a GLP-1 receptor with an affinity constant, K_D, below 1 μM, preferably below 100 nM. Methods for identifying GLP-1 agonists are described in WO 93/19175 (Novo Nordisk A/S). Examples of GLP-1 agonists to be included within the present invention are exendins as disclosed in WO 9746584 and US 5424286. US 5424286 describes a method for stimulating insulin release with exendin polypeptide(s). The exendin polypeptides disclosed include HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGX; wherein X = P or Y, and HX1X2GTFITSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS; wherein X1X2 = SD (exendin-3) or GE (exendin-4)). The exendin-3 and -4 and fragments are useful in treatment of diabetes mellitus (types I or II) and prevention of hyperglycaemia. They normalise hyperglycaemia through glucose-dependent, insulin-independent and insulin-dependent mechanisms. These insulinotropic peptides are more active than GLP-1. Exendin-4 is specific for exendin receptors, i.e. it does not interact with vasoactive intestinal peptide receptors. WO 9746584 describes truncated versions of exendin peptide(s) for treating diabetes. The disclosed peptides increase secretion and biosynthesis of insulin, but reduce those of glucagon. The truncated peptides can be made more economically than full length versions.

In the present text, the designation "an analogue" is used to designate a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide. Such addition can take place either in the peptide, at the N-terminal end or at the C-terminal end of the parent peptide, or any combination thereof.

The term "derivative" is used in the present text to designate a peptide in which one or more of the amino acid residues of the parent peptide have been chemically modified, *e.g.* by alkylation, acylation, ester formation or amide formation.

The term "a GLP-1 derivative" is used in the present text to designate a derivative of GLP-1 or an analogue thereof. In the present text, the parent peptide from which such a derivative is formally derived is in some places referred to as the "GLP-1 moiety" of the derivative.

Lipophilic Substituents

In the GLP-1 derivatives of the present invention, one or more lipophilic substituents may be attached to the parent peptide. The lipophilic substituents make the profile of action of the parent GLP-1 peptide more protracted, make the parent GLP-1 peptide more metabolically and physically stable, and/or increase the water solubility of the parent GLP-1 peptide.

The lipophilic substituent is characterised by having a solubility in water at 20°C in the range from about 0.1 mg/100 ml water to about 250 mg/100 ml water, preferable in the range from about 0.3 mg/100 ml water to about 75 mg/100 ml water. For instance, octanoic acid (C8) has a solubility in water at 20°C of 68 mg/100 ml, decanoic acid (C10) has a solubility in water at 20°C of 15 mg/100 ml, and octadecanoic acid (C18) has a solubility in water at 20°C of 0.3 mg/100 ml.

The GLP-1 derivatives of the present invention preferably have three lipophilic substituents, more preferably two lipophilic substituents, and most preferably one lipophilic substituent.

Each lipophilic substituent(s) preferably has 4-40 carbon atoms, more preferably 8-30 carbon atoms, even more preferably 8-25 carbon atoms, even more preferably 12-25 carbon atoms, and most preferably 14-18 carbon atoms.

The lipophilic substituent(s) contain a functional group which can be attached to one of the following functional groups of an amino acid of the parent GLP-1 peptide:

(a) the amino group attached to the alpha-carbon of the N-terminal amino acid,

(b) the carboxy group attached to the alpha-carbon of the C-terminal amino acid,

(c) the epsilon-amino group of any Lys residue,

(d) the carboxy group of the R group of any Asp and Glu residue,

(e) the hydroxy group of the R group of any Tyr, Ser and Thr residue,

(f) the amino group of the R group of any Trp, Asn, Gln, Arg, and His residue, or

(g) the thiol group of the R group of any Cys residue.

In an embodiment, a lipophilic substituent is attached to the carboxy group of the R group of any Asp and Glu residue.

In another embodiment, a lipophilic substituent is attached to the carboxy group attached to the alpha-carbon of the C-terminal amino acid.

In a most preferred embodiment, a lipophilic substituent is attached to the epsilon-amino group of any Lys residue.

Each lipophilic substituent contains a functional group which may be attached to a functional group of an amino acid of the parent GLP-1 peptide. For example, a lipophilic substituent may contain a carboxyl group which can be attached to an amino group of the parent GLP-1 peptide by means of an amide bond.

In an embodiment, the lipophilic substituent comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

In another embodiment, the lipophilic substituent is a straight-chain or branched alkyl group.

In another embodiment, the lipophilic substituent is an acyl group of a straight-chain or branched fatty acid. Preferably, the lipophilic substituent is an acyl group having the formula $CH_3(CH_2)_nCO$-, wherein n is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-,

$CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-. In a more preferred embodiment, the lipophilic substituent is tetradecanoyl. In a most preferred embodiment, the lipophilic substituent is hexadecanoyl.

In another embodiment of the present invention, the lipophilic substituent has a group which is negatively charged such as a carboxylic acid group. For example, the lipophilic substituent may be an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid of the formula $HOOC(CH_2)_mCO$-, wherein m is an integer from 4 to 38, preferably an integer from 12 to 38, and most preferably is $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- or $HOOC(CH_2)_{22}CO$-.

In a preferred embodiment of the invention, the lipophilic substituent is attached to the parent GLP-1 peptide by means of a spacer. A spacer must contain at least two functional groups, one to attach to a functional group of the lipophilic substituent and the other to a functional group of the parent GLP-1 peptide.

In an embodiment, the spacer is an amino acid residue except Cys or Met, or a dipeptide such as Gly-Lys. For purposes of the present invention, the phrase "a dipeptide such as Gly-Lys" means any combination of two amino acids except Cys or Met, preferably a dipeptide wherein the C-terminal amino acid residue is Lys, His or Trp, preferably Lys, and the N-terminal amino acid residue is Ala, Arg, Asp, Asn, Gly, Glu, Gln, Ile, Leu, Val, Phe, Pro, Ser, Tyr, Thr, Lys, His and Trp. Preferably, an amino group of the parent peptide forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

Preferred spacers are lysyl, glutamyl, asparagyl, glycyl, beta-alanyl and gamma-aminobutanoyl, each of which constitutes an individual embodiment. Most preferred spacers are glutamyl and beta-alanyl. When the spacer is Lys, Glu or Asp, the carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the amino group thereof may form an amide bond with a carboxyl group of the lipophilic substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the ε-amino group of Lys and the lipophilic substituent. In one embodiment, such a further spacer is succinic acid which forms an amide bond with

the ε-amino group of Lys and with an amino group present in the lipophilic substituent. In another embodiment such a further spacer is Glu or Asp which forms an amide bond with the ε-amino group of Lys and another amide bond with a carboxyl group present in the lipophilic substituent, that is, the lipophilic substituent is a N^{ε}-acylated lysine residue.

In another embodiment, the spacer is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, which spacer forms a bridge between an amino group of the parent peptide and an amino group of the lipophilic substituent. Preferably, the spacer is succinic acid.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_pNH\text{-}CO(CH_2)_qCO\text{-}$, wherein p is an integer from 8 to 33, preferably from 12 to 28 and q is an integer from 1 to 6, preferably 2.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_rCO\text{-}NHCH(COOH)(CH_2)_2CO\text{-}$, wherein r is an integer from 4 to 24, preferably from 10 to 24.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_sCO\text{-}NHCH((CH_2)_2COOH)CO\text{-}$, wherein s is an integer from 4 to 24, preferably from 10 to 24.

In a further embodiment, the lipophilic substituent is a group of the formula $COOH(CH_2)_tCO\text{-}$ wherein t is an integer from 6 to 24.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_uCH_3$, wherein u is an integer from 8 to 18.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $CH_3(CH_2)_vCO\text{-}NH\text{-}(CH_2)_z\text{-}CO$, wherein v is an integer from 4 to 24 and z is an integer from 1 to 6.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula $\text{-}NHCH(COOH)(CH_2)_4NH\text{-}COCH((CH_2)_2COOH)NH\text{-}CO(CH_2)_wCH_3$, wherein w is an integer from 10 to 16.

In a further embodiment, the lipophilic substituent with the attached spacer is a group of the formula -NHCH(COOH)$(CH_2)_4$NH-CO$(CH_2)_2$CH(COOH)NHCO$(CH_2)_x$$CH_3$, wherein x is zero or an integer from 1 to 22, preferably 10 to 16.

The term "GLP-1" means GLP-1(7-37) or GLP-1(7-36) amide.

GLP-1 analogues and derivatives which can be used according to the present invention includes those referred to in PCT/DK99/00081 (Novo Nordisk A/S), PCT/DK99/00082 (Novo Nordisk A/S), PCT/DK99/00085 (Novo Nordisk A/S), WO 98/08871 (Novo Nordisk A/S), WO 87/06941 (The General Hospital Corporation), WO 90/11296 (The General Hospital Corporation), WO 91/11457 (Buckley et al.), EP 0708179-A2 (Eli Lilly & Co.), EP 0699686-A2 (Eli Lilly & Co.) which are included herein by reference.

In one embodiment GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is GLP-1(7-37).

In another embodiment GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is GLP-1(7-36) amide.

In a further embodiment GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is an analogue of GLP-1.

In a further embodiment the analogue of GLP-1 has the formula II:

7 8 9 10 11 12 13 14 15 16 17
His-Xaa-Xaa-Gly-Xaa-Phe-Thr-Xaa-Asp-Xaa-Xaa-

18 19 20 21 22 23 24 25 26 27 28
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Phe-

29 30 31 32 33 34 35 36 37 38
Ile-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

39 40 41 42 43 44 45
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

(II)

wherein

Xaa at position 8 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, Met, or Lys,

Xaa at position 9 is Glu, Asp, or Lys,

Xaa at position 11 is Thr, Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 14 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 16 is Val, Ala, Gly, Ser, Thr, Leu, Ile, Tyr, Glu, Asp, or Lys,

Xaa at position 17 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 18 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 19 is Tyr, Phe, Trp, Glu, Asp, or Lys,

Xaa at position 20 is Leu, Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 21 is Glu, Asp, or Lys,

Xaa at position 22 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 23 is Gln, Asn, Arg, Glu, Asp, or Lys,

Xaa at position 24 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Arg, Glu, Asp, or Lys,

Xaa at position 25 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 26 is Lys, Arg, Gln, Glu, Asp, or His,

Xaa at position 27 is Glu, Asp, or Lys,

Xaa at position 30 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 31 is Trp, Phe, Tyr, Glu, Asp, or Lys,

Xaa at position 32 is Leu, Gly, Ala, Ser, Thr, Ile, Val, Glu, Asp, or Lys,

Xaa at position 33 is Val, Gly, Ala, Ser, Thr, Leu, Ile, Glu, Asp, or Lys,

Xaa at position 34 is Lys, Arg, Glu, Asp, or His,

Xaa at position 35 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 36 is Arg, Lys, Glu, Asp, or His,

Xaa at position 37 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,

Xaa at position 38 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 39 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 40 is Asp, Glu, or Lys, or is deleted,

Xaa at position 41 is Phe, Trp, Tyr, Glu, Asp, or Lys, or is deleted,

Xaa at position 42 is Pro, Lys, Glu, or Asp, or is deleted,

Xaa at position 43 is Glu, Asp, or Lys, or is deleted,

Xaa at position 44 is Glu, Asp, or Lys, or is deleted, and

Xaa at position 45 is Val, Glu, Asp, or Lys, or is deleted, or

(a) a C-1-6-ester thereof, (b) amide, C-1-6-alkylamide, or C-1-6-dialkylamide thereof and/or (c) a pharmaceutically acceptable salt thereof,

provided that

(i) when the amino acid at position 37, 38, 39, 40, 41, 42, 43 or 44 is deleted, then each amino acid downstream of the amino acid is also deleted.

In a further embodiment of the GLP-1 analogue of formula II, the amino acids at positions 37-45 are absent.

In another embodiment of the GLP-1 analogue of formula II, the amino acids at positions 38-45 are absent.

In another embodiment of the GLP-1 analogue of formula II, the amino acids at positions 39-45 are absent.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 8 is Ala, Gly, Ser, Thr, Met, or Val.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 8 is Gly, Thr, Met, or Val.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 8 is Val.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 9 is Glu.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 11 is Thr.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 14 is Ser.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 16 is Val.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 17 is Ser.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 18 is Ser, Lys, Glu, or Asp.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 19 is Tyr, Lys, Glu, or Asp.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 20 is Leu, Lys, Glu, or Asp.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 21 is Glu, Lys, or Asp.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 22 is Gly, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 23 is Gln, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 24 is Ala, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 25 is Ala, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 26 is Lys, Glu, Asp, or Arg.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 27 is Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 30 is Ala, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 31 is Trp, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 32 is Leu, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 33 is Val, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 34 is Lys, Arg, Glu, or Asp.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 35 is Gly, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 36 is Arg, Lys, Glu, or Asp.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 37 is Gly, Glu, Asp, or Lys.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 38 is Arg, or Lys, or is deleted.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 39 is deleted.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 40 is deleted.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 41 is deleted.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 42 is deleted.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 43 is deleted.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 44 is deleted.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 45 is deleted.

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 26 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 26 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 26 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 analogue of formula II, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 analogue of formula II, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 analogue of formula II, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 analogue of formula II, Xaa at positions 26 and 34 is Arg, Xaa at position 38 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at

positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 38 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 analogue of formula II, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

Such GLP-1 analogues includes, but is not limited to, Arg^{26}-GLP-1(7-37); Arg^{34}-GLP-1(7-37); Lys^{36}-GLP-1(7-37); $Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Arg^{26,34}Lys^{38}$GLP-1(7-38); $Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Arg^{26,34}Lys^{40}$-GLP-1(7-40); $Arg^{26}Lys^{36}$-GLP-1(7-37);

$Arg^{34}Lys^{36}$-GLP-1(7-37); $Arg^{26}Lys^{39}$-GLP-1(7-39); $Arg^{34}Lys^{40}$-GLP-1(7-40); $Arg^{26,34}Lys^{36,39}$-GLP-1(7-39); $Arg^{26,34}Lys^{36,40}$-GLP-1(7-40); $Gly^{8}Arg26$-GLP-1(7-37); $Gly^{8}Arg^{34}$-GLP-1(7-37); Val^{8}-GLP-1(7-37); Thr^{8}-GLP-1(7-37); Gly^{8}-GLP-1(7-37); Met^{8}-GLP-1(7-37); $Gly^{8}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{40}$-GLP-1(7-40); $Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{40}$-GLP-1(7-40); $Gly^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{36,40}$-GLP-1(7-40); $Arg^{26,34}Lys^{38}$GLP-1(7-38); $Arg^{26,34}Lys^{39}$GLP-1(7-39); $Arg^{26,34}Lys^{40}$GLP-1(7-40); $Arg^{26,34}Lys^{41}$GLP-1(7-41); $Arg^{26,34}Lys^{42}$GLP-1(7-42); $Arg^{26,34}Lys^{43}$GLP-1(7-43); $Arg^{26,34}Lys^{44}$GLP-1(7-44); $Arg^{26,34}Lys^{45}$GLP-1(7-45); $Arg^{26,34}Lys^{38}$GLP-1(1-38); $Arg^{26,34}Lys^{39}$GLP-1(1-39); $Arg^{26,34}Lys^{40}$GLP-1(1-40); $Arg^{26,34}Lys^{41}$GLP-1(1-41); $Arg^{26,34}Lys^{42}$GLP-1(1-42); $Arg^{26,34}Lys^{43}$GLP-1(1-43); $Arg^{26,34}Lys^{44}$GLP-1(1-44); $Arg^{26,34}Lys^{45}$GLP-1(1-45); $Arg^{26,34}Lys^{38}$GLP-1(2-38); $Arg^{26,34}Lys^{39}$GLP-1(2-39); $Arg^{26,34}Lys^{40}$GLP-1(2-40); $Arg^{26,34}Lys^{41}$GLP-1(2-41); $Arg^{26,34}Lys^{42}$GLP-1(2-42); $Arg^{26,34}Lys^{43}$GLP-1(2-43); $Arg^{26,34}Lys^{44}$GLP-1(2-44); $Arg^{26,34}Lys^{45}$GLP-1(2-45); $Arg^{26,34}Lys^{38}$GLP-1(3-38); $Arg^{26,34}Lys^{39}$GLP-1(3-39); $Arg^{26,34}Lys^{40}$GLP-1(3-40); $Arg^{26,34}Lys^{41}$GLP-1(3-41); $Arg^{26,34}Lys^{42}$GLP-1(3-42); $Arg^{26,34}Lys^{43}$GLP-1(3-43); $Arg^{26,34}Lys^{44}$GLP-1(3-44); $Arg^{26,34}Lys^{45}$GLP-1(3-45); $Arg^{26,34}Lys^{38}$GLP-1(4-38); $Arg^{26,34}Lys^{39}$GLP-1(4-39); $Arg^{26,34}Lys^{40}$GLP-1(4-40); $Arg^{26,34}Lys^{41}$GLP-1(4-41); $Arg^{26,34}Lys^{42}$GLP-1(4-42); $Arg^{26,34}Lys^{43}$GLP-1(4-43); $Arg^{26,34}Lys^{44}$GLP-1(4-44); $Arg^{26,34}Lys^{45}$GLP-1(4-45); $Arg^{26,34}Lys^{38}$GLP-1(5-38); $Arg^{26,34}Lys^{39}$GLP-1(5-39); $Arg^{26,34}Lys^{40}$GLP-1(5-40); $Arg^{26,34}Lys^{41}$GLP-1(5-41); $Arg^{26,34}Lys^{42}$GLP-1(5-42); $Arg^{26,34}Lys^{43}$GLP-1(5-43); $Arg^{26,34}Lys^{44}$GLP-1(5-44); $Arg^{26,34}Lys^{45}$GLP-1(5-45); $Arg^{26,34}Lys^{38}$GLP-1(6-38); $Arg^{26,34}Lys^{39}$GLP-1(6-39); $Arg^{26,34}Lys^{40}$GLP-1(6-40); $Arg^{26,34}Lys^{41}$GLP-1(6-41); $Arg^{26,34}Lys^{42}$GLP-1(6-42); $Arg^{26,34}Lys^{43}$GLP-1(6-43); $Arg^{26,34}Lys^{44}$GLP-1(6-44); $Arg^{26,34}Lys^{45}$GLP-1(6-45); $Arg^{26}Lys^{38}$GLP-1(1-38); $Arg^{34}Lys^{38}$GLP-1(1-38); $Arg^{26,34}Lys^{36,38}$GLP-1(1-38); $Arg^{26}Lys^{38}$GLP-1(7-38); $Arg^{34}Lys^{38}$GLP-1(7-38); $Arg^{26,34}Lys^{36,38}$GLP-1(7-38); $Arg^{26,34}Lys^{38}$GLP-1(7-38); $Arg^{26}Lys^{39}$GLP-1(1-39); $Arg^{34}Lys^{39}$GLP-1(1-39); $Arg^{26,34}Lys^{36,39}$GLP-1(1-39); $Arg^{26}Lys^{39}$GLP-1(7-39);

$Arg^{34}Lys^{39}$GLP-1(7-39) and $Arg^{26,34}Lys^{36,39}$GLP-1(7-39). Each one of these specific GLP-1 analogues constitutes an alternative embodiment of the invention.

GLP-1(7-37) and GLP-1(7-36) amide and the corresponding Thr^8, Met^8, Gly^8 and Val^8 analogues thereof are preferred compounds to be used according to this invention.

GLP-1(7-37) and GLP-1(7-36) amide and the corresponding Gly^8 and Val^8 analogues thereof are more preferred compounds to be used according to this invention.

Val^8GLP-1(7-37) and Val^8GLP-1(7-36) amide are still more preferred compounds to be used according to this invention.

However, protracted acting GLP-1 derivatives, in particular those described in WO 98/08871 are more preferred. The most preferred GLP-1 derivatives are those in which the parent peptide has the formula GLP-1(7-C), wherein C is 36, 37, 38, 39, 40, 41, 42, 43, 44 and 45, wherein optionally a total of up to fifteen, preferably up to ten amino acid residues have been exchanged with any α-amino acid residue which can be coded for by the genetic code, said parent peptide comprising one or two lipophilic substituents having 4 to 40 carbon atoms, preferably from 8 to 25 carbon atoms, optionally via a spacer (such as γ-Glu or β-Ala). The substituents are preferably selected from acyl groups of straight-chained or branched fatty acids.

GLP-1 analogues and derivatives that include an N-terminal imidazole group and optionally an unbranched C_6-C_{10} acyl group attached to the lysine residue in position 34 are also embodiments of the invention.

In a further embodiment GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is a GLP-1 derivative.

In a further embodiment of the GLP-1 derivative at least one amino acid residue of the parent peptide has a lipophilic substituent attached.

In a further embodiment of the GLP-1 derivative at least one amino acid residue of the parent peptide has a lipophilic substituent attached with the proviso that if only one lipophilic substituent is present and this substituent is attached to the N-terminal or to the C-terminal amino acid residue of the parent peptide then this substituent is an alkyl group or a group which has an ω-carboxylic acid group.

In another embodiment the GLP-1 derivative has only one lipophilic substituent.

In another embodiment the GLP-1 derivative has only one lipophilic substituent which substituent is an alkyl group or a group which has an ω-carboxylic acid group and is attached to the N-terminal amino acid residue of the parent peptide.

In another embodiment the GLP-1 derivative has only one lipophilic substituent which substituent is an alkyl group or a group which has an ω-carboxylic acid group and is attached to the C-terminal amino acid residue of the parent peptide.

In another embodiment the GLP-1 derivative has only one lipophilic substituent which substituent can be attached to any one amino acid residue which is not the N-terminal or C-terminal amino acid residue of the parent peptide.

In another embodiment the GLP-1 derivative has two lipophilic substituents.

In another embodiment the GLP-1 derivative has two lipophilic substituents, one being attached to the N-terminal amino acid residue while the other is attached to the C-terminal amino acid residue.

In another embodiment the GLP-1 derivative has two lipophilic substituents, one being attached to the N-terminal amino acid residue while the other is attached to an amino acid residue which is not N-terminal or the C-terminal amino acid residue.

In another embodiment the GLP-1 derivative has two lipophilic substituents, one being attached to the C-terminal amino acid residue while the other is attached to an amino acid residue which is not the N-terminal or the C-terminal amino acid residue.

In further embodiment the GLP-1 derivative is a derivative of formula GLP-1(7-C), wherein C is selected from the group comprising 38, 39, 40, 41, 42, 43, 44 and 45 which derivative has just one lipophilic substituent which is attached to the C-terminal amino acid residue of the parent peptide.

In a further embodiment of the GLP-1 derivative the lipophilic substituent comprises from 4 to 40 carbon atoms, more preferred from 8 to 25 carbon atoms.

In a further embodiment of the GLP-1 derivative the lipophilic substituent has a solubility in water at 20°C in the range from about 0.1 mg/100 ml water to about 250 mg/100 ml water, preferable in the range from about 0.3 mg/100 ml water to about 75 mg/100 ml water.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is attached to an amino acid residue in such a way that a carboxyl group of the lipophilic substituent forms an amide bond with an amino group of the amino acid residue.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is attached to an amino acid residue in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid residue.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is attached to the parent peptide by means of a spacer.

In a further embodiment the GLP-1 derivative has a lipophilic substituent, which optionally *via* a spacer is attached to the ε-amino group of a Lys residue contained in the parent peptide.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is attached to the parent peptide by means of a spacer which is an unbranched alkane α,ω-dicarboxylic acid group having from 1 to 7 methylene groups, preferably two methylene groups which spacer forms a bridge between an amino group of the parent peptide and an amino group of the lipophilic substituent.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys, or a dipeptide such as Gly-Lys.

In the present text, the expression "a dipeptide such as Gly-Lys" is used to designate a dipeptide wherein the C-terminal amino acid residue is Lys, His or Trp, preferably Lys, and wherein the N-terminal amino acid residue is selected from the group comprising Ala, Arg, Asp, Asn, Gly, Glu, Gln, Ile, Leu, Val, Phe and Pro.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys and wherein a carboxyl group of the parent peptide forms an amide bond with an amino group of a Lys residue or a dipeptide containing a Lys residue, and the other amino group of the Lys residue or a dipeptide containing a Lys residue forms an amide bond with a carboxyl group of the lipophilic substituent.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys and wherein an amino group of the parent peptide forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys and wherein a carboxyl group of the parent peptide forms an amide bond with an amino group of the amino acid residue spacer or dipeptide spacer, and the carboxyl group of the amino acid residue spacer or dipeptide spacer forms an amide bond with an amino group of the lipophilic substituent.

In a further embodiment the spacer is selected from lysyl, glutamyl, asparagyl, glycyl, beta-alanyl and gamma-aminobutanoyl. Each of these spacers constitutes an individual embodiment. Most preferred spacers are glutamyl and beta-alanyl.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys, and wherein a carboxyl group of the parent peptide forms an amide bond with an amino group of a spacer which is Asp or Glu, or a dipeptide spacer containing an Asp or Glu residue, and a carboxyl group of the spacer forms an amide bond with an amino group of the lipophilic substituent.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which comprises a partially or completely hydrogenated cyclopentanophenathrene skeleton.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is a straight-chain or branched alkyl group.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is the acyl group of a straight-chain or branched fatty acid.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is an acyl group selected from the group comprising $CH_3(CH_2)_nCO$-, wherein n is an integer from 4 to 38, preferably an integer from 4 to 24, more preferred selected from the group

comprising $CH_3(CH_2)_6CO$-, $CH_3(CH_2)_8CO$-, $CH_3(CH_2)_{10}CO$-, $CH_3(CH_2)_{12}CO$-, $CH_3(CH_2)_{14}CO$-, $CH_3(CH_2)_{16}CO$-, $CH_3(CH_2)_{18}CO$-, $CH_3(CH_2)_{20}CO$- and $CH_3(CH_2)_{22}CO$-.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is an acyl group of a straight-chain or branched alkane α,ω-dicarboxylic acid.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is an acyl group selected from the group comprising $HOOC(CH_2)_mCO$-, wherein m is an integer from 4 to 38, preferably an integer from 4 to 24, more preferred selected from the group comprising $HOOC(CH_2)_{14}CO$-, $HOOC(CH_2)_{16}CO$-, $HOOC(CH_2)_{18}CO$-, $HOOC(CH_2)_{20}CO$- and $HOOC(CH_2)_{22}CO$-.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is a group of the formula $CH_3(CH_2)_p((CH_2)_qCOOH)CHNH\text{-}CO(CH_2)_2CO$-, wherein p and q are integers and p+q is an integer of from 8 to 33, preferably from 12 to 28.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is a group of the formula $CH_3(CH_2)_rCO\text{-}NHCH(COOH)(CH_2)_2CO$-, wherein r is an integer of from 10 to 24.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is a group of the formula $CH_3(CH_2)_sCO\text{-}NHCH((CH_2)_2COOH)CO$-, wherein s is an integer of from 8 to 24.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is a group of the formula $COOH(CH_2)_tCO$- wherein t is an integer of from 8 to 24.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is a group of the formula -$NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_uCH_3$, wherein u is an integer of from 8 to 18.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is a group of the formula -$NHCH(COOH)(CH_2)_4NH\text{-}COCH((CH_2)_2COOH)NH\text{-}CO(CH_2)_wCH_3$, wherein w is an integer of from 10 to 16.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is a group of the formula -$NHCH(COOH)(CH_2)_4NH\text{-}CO(CH_2)_2CH(COOH)NH\text{-}CO(CH_2)_xCH_3$, wherein x is an integer of from 10 to 16.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which is a group of the formula -NHCH(COOH)$(CH_2)_4$NH-$CO(CH_2)_2CH(COOH)NHCO(CH_2)_yCH_3$, wherein y is zero or an integer of from 1 to 22.

In a further embodiment the GLP-1 derivative has a lipophilic substituent which can be negatively charged. Such a lipophilic substituent can for example be a substituent which has a carboxyl group.

In a further embodiment of the GLP-1 derivative the parent peptide is selected from the group comprising GLP-1(1-45) or an analogue thereof.

In a further embodiment the GLP-1 derivative is derived from a GLP-1 fragment selected from the group comprising GLP-1(7-35), GLP-1(7-36), GLP-1(7-36)amide, GLP-1(7-37), GLP-1(7-38), GLP-1(7-39), GLP-1(7-40) and GLP-1(7-41) or an analogue thereof.

In a further embodiment the GLP-1 analogue is derived from a GLP-1 analogue selected from the group comprising GLP-1(1-35), GLP-1(1-36), GLP-1(1-36)amide, GLP-1(1-37), GLP-1(1-38), GLP-1(1-39), GLP-1(1-40) and GLP-1(1-41) or an analogue thereof.

In a further embodiment of the GLP-1 derivative the designation analogue comprises derivatives wherein a total of up to fifteen, preferably up to ten amino acid residues have been exchanged with any α-amino acid residue.

In a further embodiment of the GLP-1 derivative the designation analogue comprises derivatives wherein a total of up to fifteen, preferably up to ten amino acid residues have been exchanged with any α-amino acid residue which can be coded for by the genetic code.

In a further embodiment of the GLP-1 derivative the designation analogue comprises derivatives wherein a total of up to six amino acid residues have been exchanged with another α-amino acid residue which can be coded for by the genetic code.

In a further embodiment the GLP-1 derivative is a derivative of formula GLP-1(A-B) derivative wherein A is an integer from 1 to 7 and B is an integer from 38 to 45 or an analogue thereof comprising one lipophilic substituent attached to the C-terminal

amino acid residue and, optionally, a second lipophilic substituent attached to one of the other amino acid residues.

In a further embodiment the GLP-1 derivative is a GLP-1 derivative of formula I:

7 8 9 10 11 12 13 14 15 16 17
His-Xaa-Xaa-Gly-Xaa-Phe-Thr-Xaa-Asp-Xaa-Xaa-

18 19 20 21 22 23 24 25 26 27 28
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Phe-

29 30 31 32 33 34 35 36 37 38
Ile-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

39 40 41 42 43 44 45
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

(I)

wherein

Xaa at position 8 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, Met, or Lys,

Xaa at position 9 is Glu, Asp, or Lys,

Xaa at position 11 is Thr, Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 14 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 16 is Val, Ala, Gly, Ser, Thr, Leu, Ile, Tyr, Glu, Asp, or Lys,

Xaa at position 17 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 18 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 19 is Tyr, Phe, Trp, Glu, Asp, or Lys,

Xaa at position 20 is Leu, Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 21 is Glu, Asp, or Lys,

Xaa at position 22 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 23 is Gln, Asn, Arg, Glu, Asp, or Lys,

Xaa at position 24 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Arg, Glu, Asp, or Lys,

Xaa at position 25 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 26 is Lys, Arg, Gln, Glu, Asp, or His,

Xaa at position 27 is Glu, Asp, or Lys,

Xaa at position 30 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 31 is Trp, Phe, Tyr, Glu, Asp, or Lys,

Xaa at position 32 is Leu, Gly, Ala, Ser, Thr, Ile, Val, Glu, Asp, or Lys,

Xaa at position 33 is Val, Gly, Ala, Ser, Thr, Leu, Ile, Glu, Asp, or Lys,

Xaa at position 34 is Lys, Arg, Glu, Asp, or His,

Xaa at position 35 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 36 is Arg, Lys, Glu, Asp, or His,

Xaa at position 37 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,

Xaa at position 38 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 39 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 40 is Asp, Glu, or Lys, or is deleted,

Xaa at position 41 is Phe, Trp, Tyr, Glu, Asp, or Lys, or is deleted,

Xaa at position 42 is Pro, Lys, Glu, or Asp, or is deleted,

Xaa at position 43 is Glu, Asp, or Lys, or is deleted,

Xaa at position 44 is Glu, Asp, or Lys, or is deleted, and

Xaa at position 45 is Val, Glu, Asp, or Lys, or is deleted, or

(a) a C-1-6-ester thereof, (b) amide, C-1-6-alkylamide, or C-1-6-dialkylamide thereof and/or (c) a pharmaceutically acceptable salt thereof,

provided that

(i) when the amino acid at position 37, 38, 39, 40, 41, 42, 43 or 44 is deleted, then each amino acid downstream of the amino acid is also deleted,

(ii) the derivative of the GLP-1 analog contains only one or two Lys,

(iii) the ε-amino group of one or both Lys is substituted with a lipophilic substituent optionally via a spacer,

(iv) the total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 does not exceed six.

In a further embodiment of the GLP-1 derivative of formula I, the amino acids at positions 37-45 are absent.

In another embodiment of the GLP-1 derivative of formula I, the amino acids at positions 38-45 are absent.

In another embodiment of the GLP-1 derivative of formula I, the amino acids at positions 39-45 are absent.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 8 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 8 is Ala, Gly, Ser, Thr, or Val.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 9 is Glu.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 11 is Thr.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 14 is Ser.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 16 is Val.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 17 is Ser.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 18 is Ser, Lys, Glu, or Asp.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 19 is Tyr, Lys, Glu, or Asp.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 20 is Leu, Lys, Glu, or Asp.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 21 is Glu, Lys, or Asp.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 22 is Gly, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 23 is Gln, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 24 is Ala, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 25 is Ala, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 26 is Lys, Glu, Asp, or Arg.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 27 is Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 30 is Ala, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 31 is Trp, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 32 is Leu, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 33 is Val, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 34 is Lys, Arg, Glu, or Asp.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 35 is Gly, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 36 is Arg, Lys, Glu, or Asp.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 37 is Gly, Glu, Asp, or Lys.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 38 is Arg, or Lys, or is deleted.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 39 is deleted.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 40 is deleted.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 41 is deleted.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 42 is deleted.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 43 is deleted.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 44 is deleted.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 45 is deleted.

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 26 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 26 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 26 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 derivative of formula I, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 derivative of formula I, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 derivative of formula I, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 derivative of formula I, Xaa at positions 26 and 34 is Arg, Xaa at position 38 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 38 is Lys, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 37-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 38-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another embodiment of the GLP-1 derivative of formula I, Xaa at position 8 is Thr, Ser, Gly, or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 39-45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

Such GLP-1 derivatives includes, but is not limited to,

Lys^{34} (N^{ε}-(γ-glutamyl(N^{α}-tetradecanoyl))) GLP-1 (7-37),

$Arg^{26,34}$,Lys^{8}(N^{ε}-(γ-glutamyl(N^{α}-hexadecanoyl))) GLP-1 (7-37),

Arg^{34},Lys^{26}(N^{ε}-(γ-glutamyl(N^{α}-dodecanoyl))) GLP-1 (7-37),

Arg^{34},Lys^{26}(N^{ε}-(β-alanyl(N^{α}-hexadecanoyl))) GLP-1 (7-37),

Arg^{34},Lys^{26}(N^{ε}-(α-glutamyl(N^{α}-hexadecanoyl))) GLP-1 (7-37),

Arg^{34},Lys^{26}(N^{ε}-(piperidinyl-4-carbonyl(N-hexadecanoyl))) GLP-1 (7-37),

Arg^{34},Lys^{26}(N^{ε}-(γ-glutamyl(N^{α}-decanoyl))) GLP-1 (7-37),

$Glu^{22,23,30}Arg^{26,34}Lys^{38}$($N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Glu^{23,26}Arg^{34}Lys^{38}$($N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Lys^{26,34}$-bis(N^{ε}-(γ-glutamyl(N^{α}-tetradecanoyl)))-GLP-1(7-37)-OH,

$Lys^{26,34}$-bis(N^{ε}-(γ-glutamyl(N^{α}-hexadecanoyl)))-GLP-1(7-37)-OH,

$Arg^{34}Lys^{26}$(N^{ε}-(γ-glutamyl(N^{α}-hexadecanoyl)))-GLP-1(7-37)-OH,

$Arg^{26,34}Lys^{38}$(N^{ε}-(γ-glutamyl(N^{α}-tetradecanoyl)))-GLP-1(7-38)-OH,

$Arg^{26,34}Lys^{38}$(N^{ε}-(γ-glutamyl(N^{α}-hexadecanoyl)))-GLP-1(7-38)-OH,

$Arg^{34}Lys^{26}(N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-37)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-octadecanoyl)))-GLP-1(7-38)-OH.

$Glu^{22,23,30}Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Glu^{23,26}Arg^{34}Lys^{38}(N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxytridecanoyl))-GLP-1(7-37)-OH,

$Lys^{26,34}$-bis(N^{ε}-(γ-glutamyl(N^{α}-tetradecanoyl)))-GLP-1(7-37)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(ω-carboxypentadecanoyl))-GLP-1(7-38)-OH,

$Lys^{26,34}$-bis(N^{ε}-(γ-glutamyl(N^{α}-hexadecanoyl)))-GLP-1(7-37)-OH,

$Arg^{34}Lys^{26}(N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-hexadecanoyl)))-GLP-1(7-37)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(ω-carboxypentadecanoyl))-GLP-1(7-38)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-hexadecanoyl)))-GLP-1(7-38)-OH,

$Arg^{18,23,26,30,34}Lys^{38}(N^{\varepsilon}$-hexadecanoyl)-GLP-1(7-38)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(ω-carboxytridecanoyl))-GLP-1(7-38)-OH,

$Arg^{34}Lys^{26}(N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-37)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(γ-glutamyl($N^{\alpha}$-octadecanoyl)))-GLP-1(7-38)-OH,

$Glu^{22,23,30}Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Glu^{23,26}Arg^{34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Lys^{26,34}$-bis(N^{ε}-(β-alanyl(N^{α}-tetradecanoyl)))-GLP-1(7-37)-OH,

$Lys^{26,34}$-bis(N^{ε}-(β-alanyl(N^{α}-hexadecanoyl)))-GLP-1(7-37)-OH,

$Arg^{34}Lys^{26}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-hexadecanoyl)))-GLP-1(7-37)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-hexadecanoyl)))-GLP-1(7-38)-OH,

$Arg^{34}Lys^{26}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-37)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-octadecanoyl)))-GLP-1(7-38)-OH.

$Glu^{22,23,30}Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Glu^{23,26}Arg^{34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Lys^{26,34}$-bis(N^{ε}-(β-alanyl(N^{α}-tetradecanoyl)))-GLP-1(7-37)-OH,

$Lys^{26,34}$-bis(N^{ε}-(β-alanyl(N^{α}-hexadecanoyl)))-GLP-1(7-37)-OH,

$Arg^{34}Lys^{26}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-hexadecanoyl)))-GLP-1(7-37)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-38)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-hexadecanoyl)))-GLP-1(7-38)-OH,

$Arg^{34}Lys^{26}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-tetradecanoyl)))-GLP-1(7-37)-OH,

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(β-alanyl($N^{\alpha}$-octadecanoyl)))-GLP-1(7-38)-OH,

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);

$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-37);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-37);

$Val^{8}Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);

$Val^{8}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);

$Val^{8}Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-37);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-38);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-38);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-39);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-39);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

$Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-40);

$Gly^{8}Lys^{26}$(N^{ε}-tetradecanoyl)-GLP-1(7-40);

$Gly^{8}Lys^{34}$(N^{ε}-tetradecanoyl)-GLP-1(7-40);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-40);

$Arg^{26}Lys^{34}$(N^{ε}-tetradecanoyl)-GLP-1(7-40);

Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36);

$Gly^{8}Lys^{26}$(N^{ε}-tetradecanoyl)-GLP-1(7-36);

$Gly^{8}Lys^{34}$(N^{ε}-tetradecanoyl)-GLP-1(7-36);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36);

$Arg^{26}Lys^{34}$(N^{ε}-tetradecanoyl)-GLP-1(7-36);

Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-35);

$Gly^{8}Lys^{26}$(N^{ε}-tetradecanoyl)-GLP-1(7-35);

$Gly^{8}Lys^{34}$(N^{ε}-tetradecanoyl)-GLP-1(7-35);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-35);

$Arg^{26}Lys^{34}$(N^{ε}-tetradecanoyl)-GLP-1(7-35);

Lys^{26}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

Lys^{34}(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

$Gly^{8}Lys^{26}$(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

$Gly^{8}Lys^{34}$(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

$Arg^{26}Lys^{34}$(N^{ε}-tetradecanoyl)-GLP-1(7-36)amide;

$Gly^{8}Arg^{26}Lys^{34}$(N^{ε}-tetradecanoyl)-GLP-1(7-37);

Lys^{26}(N^{ε}-tetradecanoyl)Arg^{34}-GLP-1(7-37);

$Gly^{8}Lys^{26}$(N^{ε}-tetradecanoyl)Arg^{34}-GLP-1(7-37);

$Arg^{26,34}Lys^{36}$(N^{ε}-tetradecanoyl)-GLP-1(7-37);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-37);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)Arg^{34}-GLP-1(7-38);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-tetradecanoyl)$Arg^{34}$-GLP-1(7-38);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-38);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)Arg^{34}-GLP-1(7-39);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-tetradecanoyl)$Arg^{34}$-GLP-1(7-39);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-39);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-tetradecanoyl)Arg^{34}-GLP-1(7-40);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-tetradecanoyl)$Arg^{34}$-GLP-1(7-40);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-tetradecanoyl)-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-36)amide;

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(ω-carboxynonadecanoyl))-GLP-1(7-35);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-37);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-37);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-38);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-38);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-38);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-39);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-39);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-39);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-40);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))Arg^{34}-GLP-1(7-40);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(ω-carboxynonadecanoyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-37);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-38);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-39);

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-39);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-39);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-39);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-40);

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-40);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-40);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-40);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36);

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-35);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-35);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-36)amide;

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))Arg^{34}-GLP-1(7-37);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))$Arg^{34}$-GLP-1(7-37);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-37);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-37);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))Arg^{34}-GLP-1(7-38);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))$Arg^{34}$-GLP-1(7-38);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-38);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-38);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))Arg^{34}-GLP-1(7-39);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))$Arg^{34}$-GLP-1(7-39);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-39);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-39);

$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-39);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-39);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-39);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-39);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-39);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))Arg^{34}-GLP-1(7-40);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(7-deoxycholoyl))$Arg^{34}$-GLP-1(7-40);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-40);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(7-deoxycholoyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-40);

$Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-40);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(choloyl))-GLP-1(7-40);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-40);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-40);

$Arg^{26}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-40);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36);

$Gly^{8}Lys^{26}$(N^{ε}-(choloyl))-GLP-1(7-36);

$Gly^{8}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-36);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36);

$Arg^{26}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-36);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-35);

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-35);

$Gly^{8}Lys^{26}$(N^{ε}-(choloyl))-GLP-1(7-35);

$Gly^{8}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-35);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-35);

$Arg^{26}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-35);

Lys^{26}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

Lys^{34}(N^{ε}-(choloyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{26}$(N^{ε}-(choloyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(choloyl))-GLP-1(7-36)amide;

$Arg^{26}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-36)amide;

$Gly^{8}Arg^{26}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-37);

$Gly^{8}Lys^{26}$(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-37);

$Arg^{26,34}Lys^{36}$(N^{ε}-(choloyl))-GLP-1(7-37);

$Gly^{8}Arg^{26,34}Lys^{36}$($N^{\varepsilon}$-(choloyl))-GLP-1(7-37);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-37);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-37);

$Gly^{8}Lys^{26}$(N^{ε}-(lithocholoyl))-GLP-1(7-37);

$Gly^{8}Lys^{34}$(N^{ε}-(lithocholoyl))-GLP-1(7-37);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-37);

$Arg^{26}Lys^{34}$(N^{ε}-(lithocholoyl))-GLP-1(7-37);

$Gly^{8}Arg^{26}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-38);

$Gly^{8}Lys^{26}$(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-38);

$Arg^{26,34}Lys^{36}$(N^{ε}-(choloyl))-GLP-1(7-38);

$Arg^{26,34}Lys^{38}$(N^{ε}-(choloyl))-GLP-1(7-38);

$Gly^{8}Arg^{26,34}Lys^{36}$($N^{\varepsilon}$-(choloyl))-GLP-1(7-38);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-38);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-38);

$Gly^{8}Lys^{26}$(N^{ε}-(lithocholoyl))-GLP-1(7-38);

$Gly^{8}Lys^{34}$(N^{ε}-(lithocholoyl))-GLP-1(7-38);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-38);

$Arg^{26}Lys^{34}$(N^{ε}-(lithocholoyl))-GLP-1(7-38);

$Gly^{8}Arg^{26}Lys^{34}$(N^{ε}-(choloyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-39);

$Gly^{8}Lys^{26}$(N^{ε}-(choloyl))Arg^{34}-GLP-1(7-39);

$Arg^{26,34}Lys^{36}$(N^{ε}-(choloyl))-GLP-1(7-39);

$Gly^{8}Arg^{26,34}Lys^{36}$($N^{\varepsilon}$-(choloyl))-GLP-1(7-39);

Lys^{26}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

Lys^{34}(N^{ε}-(lithocholoyl))-GLP-1(7-39);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-39);

$Gly^{8}Lys^{26}$(N^{ε}-(lithocholoyl))-GLP-1(7-39);

$Gly^{8}Lys^{34}$(N^{ε}-(lithocholoyl))-GLP-1(7-39);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-39);

$Arg^{26}Lys^{34}$(N^{ε}-(lithocholoyl))-GLP-1(7-39);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(choloyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(choloyl))Arg^{34}-GLP-1(7-40);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(choloyl))$Arg^{34}$-GLP-1(7-40);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(choloyl))-GLP-1(7-40);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(choloyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-40);

$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-40);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-40);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-40);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-40);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-40);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36);

$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-35);

$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-35);

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-35);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-35);

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-35);

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-35);

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-35);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36)amide;

$Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36)amide;

$Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36)amide;

$Gly^{8}Lys^{26,34}$-bis(N^{ε}-(lithocholoyl))-GLP-1(7-36)amide;

$Arg^{26}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-36)amide;

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))Arg^{34}-GLP-1(7-37);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(lithocholoyl))$Arg^{34}$-GLP-1(7-37);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-37);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-38);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))Arg^{34}-GLP-1(7-38);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(lithocholoyl))$Arg^{34}$-GLP-1(7-38);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-38);

$Arg^{26,34}Lys^{38}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-38);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-38);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-39);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))Arg^{34}-GLP-1(7-39);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(lithocholoyl))$Arg^{34}$-GLP-1(7-39);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-39);

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-39);

$Gly^{8}Arg^{26}Lys^{34}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-40);

$Lys^{26}(N^{\varepsilon}$-(lithocholoyl))Arg^{34}-GLP-1(7-40);

$Gly^{8}Lys^{26}(N^{\varepsilon}$-(lithocholoyl))$Arg^{34}$-GLP-1(7-40);

$Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-40) and

$Gly^{8}Arg^{26,34}Lys^{36}(N^{\varepsilon}$-(lithocholoyl))-GLP-1(7-40). Each one of these specific GLP-1 derivatives constitutes an alternative embodiment of the invention.

The most preferred GLP-1 derivative is Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37).

In a further embodiment of the GLP-1 derivative, a parent peptide for a derivative of the invention is

Arg^{26}-GLP-1(7-37); Arg^{34}-GLP-1(7-37); Lys^{36}-GLP-1(7-37); $Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Arg^{26,34}Lys^{38}$GLP-1(7-38); $Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Arg^{26,34}Lys^{40}$-GLP-1(7-40); $Arg^{26}Lys^{36}$-GLP-1(7-37); $Arg^{34}Lys^{36}$-GLP-1(7-37); $Arg^{26}Lys^{39}$-GLP-1(7-39); $Arg^{34}Lys^{40}$-GLP-1(7-40); $Arg^{26,34}Lys^{36,39}$-GLP-1(7-39); $Arg^{26,34}Lys^{36,40}$-GLP-1(7-40); $Gly^{8}Arg^{26}$-GLP-1(7-37); $Gly^{8}Arg^{34}$-GLP-1(7-37); $Gly^{8}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{40}$-GLP-1(7-40); $Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{40}$-GLP-1(7-40); $Gly^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{36,40}$-GLP-1(7-40); $Val^{8}Arg^{26}$-GLP-1(7-37); $Val^{8}Arg^{34}$-GLP-1(7-37); $Val^{8}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{40}$-GLP-1(7-40); $Val^{8}Arg^{26}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{34}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{26}Lys^{39}$-GLP-1(7-39); $Val^{8}Arg^{34}Lys^{40}$-GLP-1(7-40); $Val^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39); or $Val^{8}Arg^{26,34}Lys^{36,40}$-GLP-1(7-40).

In a further embodiment, a parent peptide for a derivative of the invention is: $Arg^{26,34}Lys^{38}$GLP-1(7-38); $Arg^{26,34}Lys^{39}$GLP-1(7-39); $Arg^{26,34}Lys^{40}$GLP-1(7-40); $Arg^{26,34}Lys^{41}$GLP-1(7-41); $Arg^{26,34}Lys^{42}$GLP-1(7-42); $Arg^{26,34}Lys^{43}$GLP-1(7-43); $Arg^{26,34}Lys^{44}$GLP-1(7-44); $Arg^{26,34}Lys^{45}$GLP-1(7-45); $Arg^{26}Lys^{38}$GLP-1(7-38); $Arg^{34}Lys^{38}$GLP-1(7-38); $Arg^{26,34}Lys^{36,38}$GLP-1(7-38); $Arg^{26,34}Lys^{38}$GLP-1(7-38); $Arg^{26}Lys^{39}$GLP-1(1-39); $Arg^{34}Lys^{39}$GLP-1(1-39); $Arg^{26,34}Lys^{36,39}$GLP-1(1-39); $Arg^{26}Lys^{39}$GLP-1(7-39); $Arg^{34}Lys^{39}$GLP-1(7-39); $Arg^{26,34}Lys^{36,39}$GLP-1(7-39).

In a further embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising Arg^{26}-GLP-1(7-37), Arg^{34}-GLP-1(7-37), Lys^{36}-GLP-1(7-37), $Arg^{26,34}Lys^{36}$-GLP-1(7-37), $Arg^{26}Lys^{36}$-GLP-1(7-37), $Arg^{34}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26}$-GLP-1(7-37), $Gly^{8}Arg^{34}$-GLP-1(7-37), $Gly^{8}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37), $Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-37) and $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-37).

In a further embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising $Arg^{26}Lys^{38}$-GLP-1(7-38), $Arg^{26,34}Lys^{38}$-GLP-1(7-38), $Arg^{26,34}Lys^{36,38}$-GLP-1(7-38), $Gly^{8}Arg^{26}Lys^{38}$-GLP-1(7-38) and $Gly^{8}Arg^{26,34}Lys^{36,38}$-GLP-1(7-38).

In a further embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising $Arg^{26}Lys^{39}$-GLP-1(7-39), $Arg^{26,34}Lys^{36,39}$-GLP-1(7-39), $Gly^{8}Arg^{26}Lys^{39}$-GLP-1(7-39) and $Gly^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39).

In a further embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising $Arg^{34}Lys^{40}$-GLP-1(7-40), $Arg^{26,34}Lys^{36,40}$-GLP-1(7-40), $Gly^{8}Arg^{34}Lys^{40}$-GLP-1(7-40) and $Gly^{8}Arg^{26,34}Lys^{36,40}$-GLP-1(7-40).

In a further embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is:

Arg^{26}-GLP-1(7-36); Arg^{34}-GLP-1(7-36); $Arg^{26,34}Lys^{36}$-GLP-1(7-36); Arg^{26}-GLP-1(7-36)amide; Arg^{34}-GLP-1(7-36)amide; $Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; Arg^{26}-GLP-1(7-37); Arg^{34}-GLP-1(7-37); $Arg^{26,34}Lys^{36}$-GLP-1(7-37); Arg^{26}-GLP-1(7-38); Arg^{34}-GLP-1(7-38) ; $Arg^{26,34}Lys^{38}$GLP-1(7-38); Arg^{26}-GLP-1(7-39); Arg^{34}-GLP-1(7-39); $Arg^{26,34}Lys^{39}$-GLP-1(7-39);

$Gly^{8}Arg^{26}$-GLP-1(7-36); $Gly^{8}Arg^{34}$-GLP-1(7-36); $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Gly^{8}Arg^{26}$-GLP-1(7-36)amide; $Gly^{8}Arg^{34}$-GLP-1(7-36)amide; $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Gly^{8}Arg^{26}$-GLP-1(7-37); $Gly^{8}Arg^{34}$-GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26}$-GLP-1(7-38); $Gly^{8}Arg^{34}$-GLP-1(7-38) ; $Gly^{8}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Gly^{8}Arg^{26}$-GLP-1(7-39); $Gly^{8}Arg^{34}$-GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39);

$Val^{8}Arg^{26}$-GLP-1(7-36); $Val^{8}Arg^{34}$-GLP-1(7-36); $Val^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Val^{8}Arg^{26}$-GLP-1(7-36)amide; $Val^{8}Arg^{34}$-GLP-1(7-36)amide; $Val^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Val^{8}Arg^{26}$-GLP-1(7-37); $Val^{8}Arg^{34}$-GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{26}$-GLP-1(7-38); $Val^{8}Arg^{34}$-GLP-1(7-38); $Val^{8}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Val^{8}Arg^{26}$-GLP-1(7-39); $Val^{8}Arg^{34}$-GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39);

$Ser^{8}Arg^{26}$-GLP-1(7-36); $Ser^{8}Arg^{34}$-GLP-1(7-36); $Ser^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Arg^{26}$-GLP-1(7-36)amide; $Ser^{8}Arg^{34}$-GLP-1(7-36)amide; $Ser^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Ser^{8}Arg^{26}$-GLP-1(7-37); $Ser^{8}Arg^{34}$-GLP-1(7-37); $Ser^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Ser^{8}Arg^{26}$-GLP-1(7-38); $Ser^{8}Arg^{34}$-GLP-1(7-38) ; $Ser^{8}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Arg^{26}$-GLP-1(7-39); $Ser^{8}Arg^{34}$-GLP-1(7-39); $Ser^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39);

$Thr^{8}Arg^{26}$-GLP-1(7-36); $Thr^{8}Arg^{34}$-GLP-1(7-36); $Thr^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Arg^{26}$-GLP-1(7-36)amide; $Thr^{8}Arg^{34}$-GLP-1(7-36)amide; $Thr^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Thr^{8}Arg^{26}$-GLP-1(7-37); $Thr^{8}Arg^{34}$-GLP-1(7-37); $Thr^{8}Arg^{26,34}Lys^{36}$-GLP-1(7-37); $Thr^{8}Arg^{26}$-GLP-1(7-38); $Thr^{8}Arg^{34}$-GLP-1(7-38) ; $Thr^{8}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Thr^{8}Arg^{26}$-GLP-1(7-39); $Thr^{8}Arg^{34}$-GLP-1(7-39); $Thr^{8}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Val^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Val^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Val^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Val^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Val^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Val^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Val^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Val^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Val^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Val^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Val^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Val^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Val^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Val^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Val^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Val^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Val^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Val^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Val^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Val^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Ser^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Ser^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Ser^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Ser^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Ser^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Ser^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Ser^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Ser^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Ser^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Ser^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Ser^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Ser^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Ser^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Ser^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Thr^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Thr^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Thr^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Thr^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Thr^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Thr^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Thr^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Thr^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39);

$Thr^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Thr^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Thr^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Thr^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Thr^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Thr^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Thr^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Thr^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Thr^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Gly^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Gly^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Gly^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Gly^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Gly^{8}Glu^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Gly^{8}Glu^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Gly^{8}Glu^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Gly^{8}Glu^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Gly^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Gly^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Gly^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Gly^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36); $Gly^{8}Asp^{35}Arg^{26,34}Lys^{36}$-GLP-1(7-36)amide; $Gly^{8}Asp^{36}Arg^{26,34}Lys^{37}$GLP-1(7-37); $Gly^{8}Asp^{37}Arg^{26,34}Lys^{38}$GLP-1(7-38); $Gly^{8}Asp^{38}Arg^{26,34}Lys^{39}$-GLP-1(7-39); $Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{18}$GLP-1(7-37); $Arg^{26,34}Lys^{18}$GLP-1(7-38); $Gly^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Gly^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Gly^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Gly^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Gly^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-37); $Gly^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-38); $Gly^{8}Asp^{17}Arg^{26,34}Lys^{18}$GLP-1(7-38); $Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{23}$GLP-1(7-37); $Arg^{26,34}Lys^{23}$GLP-1(7-38); $Gly^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Gly^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Gly^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Gly^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Gly^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Gly^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-38); $Gly^{8}Asp^{22}Arg^{26,34}Lys^{23}$GLP-1(7-38); $Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{27}$GLP-1(7-37); $Arg^{26,34}Lys^{27}$GLP-1(7-38); $Gly^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Gly^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Gly^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Gly^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Gly^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Gly^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-38); $Gly^{8}Asp^{26}Arg^{26,34}Lys^{27}$GLP-1(7-38);

$Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{18}$GLP-1(7-37); $Arg^{26,34}Lys^{18}$GLP-1(7-38); $Val^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Val^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Val^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Val^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Val^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-37); $Val^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-38); $Val^{8}Asp^{17}Arg^{26,34}Lys^{18}$GLP-1(7-38);

$Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{23}$GLP-1(7-37); $Arg^{26,34}Lys^{23}$GLP-1(7-38); $Val^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Val^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Val^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Val^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Val^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Val^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-38); $Val^{8}Asp^{22}Arg^{26,34}Lys^{23}$GLP-1(7-38);

$Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{27}$GLP-1(7-37); $Arg^{26,34}Lys^{27}$GLP-1(7-38); $Val^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Val^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Val^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Val^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Val^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Val^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-38); $Val^{8}Asp^{26}Arg^{26,34}Lys^{27}$GLP-1(7-38);

$Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{18}$GLP-1(7-37); $Arg^{26,34}Lys^{18}$GLP-1(7-38); $Ser^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Ser^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Ser^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Ser^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Ser^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-37); $Ser^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-38); $Ser^{8}Asp^{17}Arg^{26,34}Lys^{18}$GLP-1(7-38);

$Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{23}$GLP-1(7-37); $Arg^{26,34}Lys^{23}$GLP-1(7-38); $Ser^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Ser^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Ser^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Ser^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Ser^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Ser^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-38); $Ser^{8}Asp^{22}Arg^{26,34}Lys^{23}$GLP-1(7-38);

$Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{27}$GLP-1(7-37); $Arg^{26,34}Lys^{27}$GLP-1(7-38); $Ser^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Ser^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Ser^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Ser^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Ser^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Ser^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-38); $Ser^{8}Asp^{26}Arg^{26,34}Lys^{27}$GLP-1(7-38);

$Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{18}$GLP-1(7-37); $Arg^{26,34}Lys^{18}$GLP-1(7-38); $Thr^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Thr^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36); $Thr^{8}Asp^{19}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Thr^{8}Asp^{17}Arg^{26,34}Lys^{18}$-GLP-1(7-36)amide; $Thr^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-37); $Thr^{8}Asp^{19}Arg^{26,34}Lys^{18}$GLP-1(7-38); $Thr^{8}Asp^{17}Arg^{26,34}Lys^{18}$GLP-1(7-38);

$Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{23}$GLP-1(7-37); $Arg^{26,34}Lys^{23}$GLP-1(7-38); $Thr^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Thr^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36); $Thr^{8}Asp^{24}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Thr^{8}Asp^{22}Arg^{26,34}Lys^{23}$-GLP-1(7-36)amide; $Thr^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Thr^{8}Asp^{24}Arg^{26,34}Lys^{23}$GLP-1(7-38); $Thr^{8}Asp^{22}Arg^{26,34}Lys^{23}$GLP-1(7-38);

$Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Arg^{26,34}Lys^{27}$GLP-1(7-37); $Arg^{26,34}Lys^{27}$GLP-1(7-38); $Thr^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Thr^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36); $Thr^{8}Asp^{28}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Thr^{8}Asp^{26}Arg^{26,34}Lys^{27}$-GLP-1(7-36)amide; $Thr^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Thr^{8}Asp^{28}Arg^{26,34}Lys^{27}$GLP-1(7-38); $Thr^{8}Asp^{26}Arg^{26,34}Lys^{27}$GLP-1(7-38).

In a further embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is:

$Arg^{26}Lys^{36}$-GLP-1(7-36); $Arg^{34}Lys^{36}$-GLP-1(7-36); $Arg^{26}Lys^{36}$-GLP-1(7-37); $Arg^{34}Lys^{36}$-GLP-1(7-37); $Arg^{26}Lys^{37}$-GLP-1(7-37); $Arg^{34}Lys^{37}$-GLP-1(7-37); $Arg^{26}Lys^{39}$-GLP-1(7-39); $Arg^{34}Lys^{39}$-GLP-1(7-39); $Arg^{26,34}Lys^{36,39}$-GLP-1(7-39);

$Arg^{26}Lys^{18}$-GLP-1(7-36); $Arg^{34}Lys^{18}$-GLP-1(7-36); $Arg^{26}Lys^{18}$GLP-1(7-37); $Arg^{34}Lys^{18}$GLP-1(7-37); $Arg^{26}Lys^{18}$GLP-1(7-38); $Arg^{34}Lys^{18}$GLP-1(7-38); $Arg^{26}Lys^{18}$GLP-1(7-39); $Arg^{34}Lys^{18}$GLP-1(7-39);

$Arg^{26}Lys^{23}$-GLP-1(7-36); $Arg^{34}Lys^{23}$-GLP-1(7-36); $Arg^{26}Lys^{23}$GLP-1(7-37); $Arg^{34}Lys^{23}$GLP-1(7-37); $Arg^{26}Lys^{23}$GLP-1(7-38); $Arg^{34}Lys^{23}$GLP-1(7-38); $Arg^{26}Lys^{23}$GLP-1(7-39); $Arg^{34}Lys^{23}$GLP-1(7-39);

$Arg^{26}Lys^{27}$-GLP-1(7-36); $Arg^{34}Lys^{27}$-GLP-1(7-36); $Arg^{26}Lys^{27}$GLP-1(7-37); $Arg^{34}Lys^{27}$GLP-1(7-37); $Arg^{26}Lys^{27}$GLP-1(7-38); $Arg^{34}Lys^{27}$GLP-1(7-38); $Arg^{26}Lys^{27}$GLP-1(7-39); $Arg^{34}Lys^{27}$GLP-1(7-39);

$Arg^{26,34}Lys^{18,36}$-GLP-1(7-36); $Arg^{26,34}Lys^{18}$GLP-1(7-37); $Arg^{26,34}Lys^{18,37}$GLP-1(7-37); $Arg^{26,34}Lys^{18,38}$GLP-1(7-38); $Arg^{26,34}Lys^{18,39}$GLP-1(7-39); $Arg^{26,34}Lys^{23,36}$-GLP-1(7-36); $Arg^{26,34}Lys^{23}$GLP-1(7-37); $Arg^{26,34}Lys^{23,37}$GLP-1(7-37); $Arg^{26,34}Lys^{23,38}$GLP-1(7-38); $Arg^{26,34}Lys^{23,39}$GLP-1(7-39); $Arg^{26,34}Lys^{27,36}$-GLP-1(7-36); $Arg^{26,34}Lys^{27}$GLP-1(7-37); $Arg^{26,34}Lys^{27,37}$GLP-1(7-37); $Arg^{26,34}Lys^{27,38}$GLP-1(7-38); $Arg^{26,34}Lys^{27,39}$GLP-1(7-39); Gly^{8}GLP-1(7-36); Gly^{8}GLP-1(7-37); Gly^{8}GLP-1(7-38); Gly^{8}GLP-1(7-39)

$Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-36); $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-36); $Gly^{8}Arg^{26}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{36}$-GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{37}$-GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{37}$-GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{39}$-GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39);

$Gly^{8}Arg^{26}Lys^{18}$-GLP-1(7-36); $Gly^{8}Arg^{34}Lys^{18}$-GLP-1(7-36); $Gly^{8}Arg^{26}Lys^{18}$GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{18}$GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{18}$GLP-1(7-38); $Gly^{8}Arg^{34}Lys^{18}$GLP-1(7-38); $Gly^{8}Arg^{26}Lys^{18}$GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{18}$GLP-1(7-39);

$Gly^{8}Arg^{26}Lys^{23}$-GLP-1(7-36); $Gly^{8}Arg^{34}Lys^{23}$-GLP-1(7-36); $Gly^{8}Arg^{26}Lys^{23}$GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{23}$GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{23}$GLP-1(7-38); $Gly^{8}Arg^{34}Lys^{23}$GLP-1(7-38); $Gly^{8}Arg^{26}Lys^{23}$GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{23}$GLP-1(7-39);

$Gly^{8}Arg^{26}Lys^{27}$-GLP-1(7-36); $Gly^{8}Arg^{34}Lys^{27}$-GLP-1(7-36); $Gly^{8}Arg^{26}Lys^{27}$GLP-1(7-37); $Gly^{8}Arg^{34}Lys^{27}$GLP-1(7-37); $Gly^{8}Arg^{26}Lys^{27}$GLP-1(7-38); $Gly^{8}Arg^{34}Lys^{27}$GLP-1(7-38); $Gly^{8}Arg^{26}Lys^{27}$GLP-1(7-39); $Gly^{8}Arg^{34}Lys^{27}$GLP-1(7-39);

$Gly^{8}Arg^{26,34}Lys^{18,36}$-GLP-1(7-36); $Gly^{8}Arg^{26,34}Lys^{18}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{18,37}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{18,38}$GLP-1(7-38); $Gly^{8}Arg^{26,34}Lys^{18,39}$GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{23,36}$-GLP-1(7-36); $Gly^{8}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{23,37}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{23,38}$GLP-1(7-38); $Gly^{8}Arg^{26,34}Lys^{23,39}$GLP-1(7-39); $Gly^{8}Arg^{26,34}Lys^{27,36}$-GLP-1(7-36); $Gly^{8}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{27,37}$GLP-1(7-37); $Gly^{8}Arg^{26,34}Lys^{27,38}$GLP-1(7-38); $Gly^{8}Arg^{26,34}Lys^{27,39}$GLP-1(7-39); Val^{8}GLP-1(7-36); Val^{8}GLP-1(7-37); Val^{8}GLP-1(7-38); Val^{8}GLP-1(7-39)

$Val^{8}Arg^{26}Lys^{36}$-GLP-1(7-36); $Val^{8}Arg^{34}Lys^{36}$-GLP-1(7-36); $Val^{8}Arg^{26}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{34}Lys^{36}$-GLP-1(7-37); $Val^{8}Arg^{26}Lys^{37}$-GLP-1(7-37); $Val^{8}Arg^{34}Lys^{37}$-GLP-1(7-37); $Val^{8}Arg^{26}Lys^{39}$-GLP-1(7-39); $Val^{8}Arg^{34}Lys^{39}$-GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{36,39}$-GLP-1(7-39);

$Val^{8}Arg^{26}Lys^{18}$-GLP-1(7-36); $Val^{8}Arg^{34}Lys^{18}$-GLP-1(7-36); $Val^{8}Arg^{26}Lys^{18}$GLP-1(7-37); $Val^{8}Arg^{34}Lys^{18}$GLP-1(7-37); $Val^{8}Arg^{26}Lys^{18}$GLP-1(7-38); $Val^{8}Arg^{34}Lys^{18}$GLP-1(7-38); $Val^{8}Arg^{26}Lys^{18}$GLP-1(7-39); $Val^{8}Arg^{34}Lys^{18}$GLP-1(7-39); $Val^{8}Arg^{26}Lys^{23}$-GLP-1(7-36); $Val^{8}Arg^{34}Lys^{23}$-GLP-1(7-36); $Val^{8}Arg^{26}Lys^{23}$GLP-1(7-37); $Val^{8}Arg^{34}Lys^{23}$GLP-1(7-37); $Val^{8}Arg^{26}Lys^{23}$GLP-1(7-38); $Val^{8}Arg^{34}Lys^{23}$GLP-1(7-38); $Val^{8}Arg^{26}Lys^{23}$GLP-1(7-39); $Val^{8}Arg^{34}Lys^{23}$GLP-1(7-39); $Val^{8}Arg^{26}Lys^{27}$-GLP-1(7-36); $Val^{8}Arg^{34}Lys^{27}$-GLP-1(7-36); $Val^{8}Arg^{26}Lys^{27}$GLP-1(7-37); $Val^{8}Arg^{34}Lys^{27}$GLP-1(7-37); $Val^{8}Arg^{26}Lys^{27}$GLP-1(7-38); $Val^{8}Arg^{34}Lys^{27}$GLP-1(7-38); $Val^{8}Arg^{26}Lys^{27}$GLP-1(7-39); $Val^{8}Arg^{34}Lys^{27}$GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{18,36}$-GLP-1(7-36); $Val^{8}Arg^{26,34}Lys^{18}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{18,37}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{18,38}$GLP-1(7-38); $Val^{8}Arg^{26,34}Lys^{18,39}$GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{23,36}$-GLP-1(7-36); $Val^{8}Arg^{26,34}Lys^{23}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{23,37}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{23,38}$GLP-1(7-38); $Val^{8}Arg^{26,34}Lys^{23,39}$GLP-1(7-39); $Val^{8}Arg^{26,34}Lys^{27,36}$-GLP-1(7-36); $Val^{8}Arg^{26,34}Lys^{27}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{27,37}$GLP-1(7-37); $Val^{8}Arg^{26,34}Lys^{27,38}$GLP-1(7-38); $Val^{8}Arg^{26,34}Lys^{27,39}$GLP-1(7-39).

In a further embodiment GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is a GLP-1 agonist.

In a further embodiment the GLP-1 agonist is a molecule, preferably a non-peptide, which binds to a GLP-1 receptor with an affinity constant, K_D, below 1 μM, preferably below 100 nM.

In a further embodiment the GLP-1 agonist is selected from exendin as well as analogs, derivatives, and fragments thereof, preferably exendin-3 and -4.

Any possible combination of two or more of the embodiments described herein, is comprised within the scope of the present invention.

For a description of suitable dosage forms, dosage ranges, pharmaceutical formulations etc. reference is made to WO 98/08871 (Novo Nordisk A/S).

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral.

Pharmaceutical compositions (or medicaments) containing GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist, may be administered parenterally to patients in need of such a treatment. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. A further option is a composition which may be a powder or a liquid for the administration of the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist in the form of a nasal or pulmonal spray. As a still further option, the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist can also be administered transdermally, *e.g.* from a patch, optionally a iontophoretic patch, or transmucosally, *e.g.* bucally. As a still further option, the GLP-1 or an analogue or a GLP-1 agonist can also be administered by gene therapy, such as by implanting a cell line transformed with a vector such that it secretes the GLP-1 or an analogue or a GLP-1 agonist. The implanted cells may be encapsulated in semi permeable membranes, e.g. macro- or microencapsulated. The above mentioned possible ways to administer GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist are not considered as limiting the scope of the invention.

Pharmaceutical compositions containing GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist may be prepared by conventional techniques, *e.g.* as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995.

Thus, the injectable compositions of the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist can be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the ingredients as appropriate to give the desired end product.

According to one procedure, the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is dissolved in an amount of water which is somewhat less than the final volume of the composition to be prepared. An isotonic agent, a preservative and a buffer is added as required and the pH value of the solution is adjusted - if necessary - using an acid, *e.g.* hydrochloric acid, or a base, *e.g.* aqueous sodium hydroxide as needed. Finally,

the volume of the solution is adjusted with water to give the desired concentration of the ingredients.

Examples of isotonic agents are sodium chloride, mannitol and glycerol.

Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate and benzyl alcohol.

Examples of suitable buffers are sodium acetate and sodium phosphate.

Further to the above-mentioned components, solutions containing a GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist may also contain a surfactant in order to improve the solubility and/or the stability of the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist.

A composition for nasal administration of certain peptides may, for example, be prepared as described in European Patent No. 272097 (to Novo Nordisk A/S) or in WO 93/18785.

According to one embodiment of the present invention, the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is provided in the form of a composition suitable for administration by injection. Such a composition can either be an injectable solution ready for use or it can be an amount of a solid composition, *e.g.* a lyophilised product, which has to be dissolved in a solvent before it can be injected. The injectable solution preferably contains not less than about 2 mg/ml, preferably not less than about 5 mg/ml, more preferred not less than about 10 mg/ml of the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist and, preferably, not more than about 100 mg/ml of the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist.

The GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist can be used in the treatment of various diseases. The particular GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to be used and the optimal dose level for any patient will depend on the disease to be treated and on a variety of factors including the efficacy of the specific peptide derivative employed, the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity of the case. It is recommended that the dosage of the GLP-1 or an analogue or a

derivative thereof or a GLP-1 agonist be determined for each individual patient by those skilled in the art.

Example 1

The protocol was a slight modification of the procedure described by Billestrup and Nielsen (Billestrup N, Nielsen JH: The stimulatory effect of growth hormone, prolactin, and placental lactogen on beta cell proliferation is not mediated by insulin-like growth factor-I. Endocrinology 1991; 129:883-888.). Pancreatic islets were isolated from newborn rats by the collagenase method and cultured for 2-5 days before use. 2000 islets were transfered to 15 ml plastic tubes and washed once with Ca/Mg-free Hank's balanced salt solution. 500 µl cold trypsin solution (0.05% trypsin, 0.53 mM EDTA in Ca/Mg-free Hank's solution). The islets were dispersed by aspiration with a pipette. 5 ml culture medium RPMI 1640 with 2% human serum was added. 75,000 islet cells were then placed in tissue culture flasks previously coated with ECL cell attachment matrix (Upstate Biotechnology) with 2 ml culture medium with 1 µg/ml human growth hormone (hGH) (Norditropin, Novo Nordisk). After 7 days in culture at 37C the medium was replaced with culture medium without hGH or with addition of 100nM GLP-1, 5 µM Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) or 200 ng/ml hGH. After 2 days in culture 10 µM 5-bromo-2-deoxyuridine (BrdU) was added and after 90 min the medium was removed and the cells fixed in 1% paraformaldehyde in 0.1 M phosphate buffer. The cells were then stained with antibodies to BrdU and insulin as described (Billestrup and Nielsen, 1991). The number of labelled beta cells in the absence of hormones was 0.6% and in the presence of hGH 3.5%. In the presence of GLP-1 the number was 1.7% and in the presence of Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) 1.4%.

Example 2

The male Zucker Diabetic Fatty fa/fa (ZDF) rat is a model of Type 2 diabetes. The rats are insulin resistant but normoglycemic from birth and they develop diabetes from about week 7 to week 10 of age. During the transitional period, the animals go through a state of impaired glucose tolerance. Although the animals are hyperinsulinemic before diabetes onset and during the early stages of diabetes, they later lose glucose-stimulated insulin secretion and finally become almost completely insulinopenic.

We have studied the effects of Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) therapy during a period of time when the animals would normally progress from having impaired glucose tolerance to having overt Type 2 diabetes. Three groups of male ZDF rats (Genetic Models Inc, Indianapolis, Indiana, USA) were studied and dosed subcutaneously bi-daily with either vehicle (group A), 30 (group B) or 150 μg/kg (group C) of Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), n=6 per group. Animals were between 7 and 8 weeks old when dosing was initiated, and fed glucose levels were not different between the groups before dosing began. However, they were elevated compared to a group of non-diabetic Sprague-Dawley rats who had fed glucose levels significantly below the ZDF animals (6.4±0.6 vs 5.8±0.8, mean±SD, $p<0.02$). This demonstrates the relative impaired glucose tolerant state of the ZDF animals when the study began. After 10 days of dosing, group C had blood glucose levels during a normal 24-hour feeding schedule that were unchanged compared to the initial measurements and they were significantly lower than the vehicle- and low-dose-treated animals who were hyperglycemic (Fig 1, $p<0.0002$ by ANOVA, total area under the curve used as summary measure). After 36 days of dosing, an oral glucose tolerance test was performed in the animals after an 11-hour fast. One g/kg of glucose was administered by oral gavage and subsequent measurements of blood glucose and plasma insulin were made. Also in this test, the glycemic level was significantly lower in group C compared to groups A and B (Fig 2 upper panel, $p<0.0002$ by ANOVA, total area under the curve used as summary measure. These results demonstrate that treatment with Arg^{34},

Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) can prevent or delay the progression of impaired glucose tolerance to Type 2 diabetes.

Example 3

The rat experiment described in example 2 were examined for effects of Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) (named GLP1 in fig. 3 and 4) on beta-cell growth and neogenesis.

Bromodeoxyuridine (BrDU) is incorporated in newly synthesized DNA and thus will label replicating cells. Six hours before sacrifice the rats were given an injection of 100 mg BrDU/kg intraperitoneally. After sacrifice the pancreata were fixed in 4% PFA, dehydrated, embedded in paraffin, and 3-4 mm sections double stained for BrDU and insulin for the measurement of beta-cell proliferation rate.

Insulin was stained with guinea pig anti-insulin, peroxidase-coupled rabbit anti-guinea pig Ig, and developed with AEC to give a red stain. BrDU was stained by monoclonal mouse anti-BrDU, biotinylated goat anti-mouse Ig, avidin peroxidase, and developed with DAB and $CuSO_4$ to give a dark brown stain. BrDU stained nuclei of cells with insulin stained cytoplasm was examined in more than 1500 cells per section. The examination of the sections were carried out with the origin of the sections blinded to the observer.

The rats treated with Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) showed a dose dependent increase in the fraction of beta-cells that had incorporated BrDU as a result of stimulated cell proliferation.

Neighbor sections were stained for insulin and the combination of glucagon-somatostatin-pancreatic polypeptide for the measurement of the relative mass of islet beta-cells and nonbeta-cells. The beta-cells were stained for insulin as described above. The nonbeta-cells were stained with a mixture of monoclonal mouse anti-glucagon +

rabbit anti-somatostatin + rabbit anti-pancreatic polypeptide, detected by biotinylated swine anti-multible Ig's, avidin peroxidase, and developed with DAB and $CuSO_4$ to give a dark brown stain. The volume fractions of beta- and nonbeta-cells were estimated by point counting stereologic techniques.

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The beta-cell fraction of the total pancreas was significantly higher in the rats given Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) at 30 ng/g for 6 weeks compared to vehicle treated rats, while there was no further increase in rats given doses of 150 ng/g.

Claims

1. Use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for delaying the progression of impaired glucose tolerance (IGT) to insulin requiring Type II diabetes.

2. Use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for increasing the insulin synthesis capability of a subject.

3. Use of GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist for the preparation of a medicament for delaying the progression of non-insulin requiring Type II diabetes to insulin requiring Type II diabetes.

4. The use according to claim 1, 2 or 3 wherein the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is a GLP-1 derivative wherein at least one amino acid residue of the parent peptide has a lipophilic substituent attached.

5. The use according to claim 4 wherein the GLP-1 derivative is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

6. The use according to claim 1, 2 or 3 wherein the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is selected from GLP-1(7-37) and GLP-1(7-36) amide and the corresponding Thr^8, Met^8, Gly^8 and Val^8 analogues.

7. A method of delaying the progression of impaired glucose tolerance (IGT) to insulin requiring Type II diabetes comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to a subject suffering from IGT.

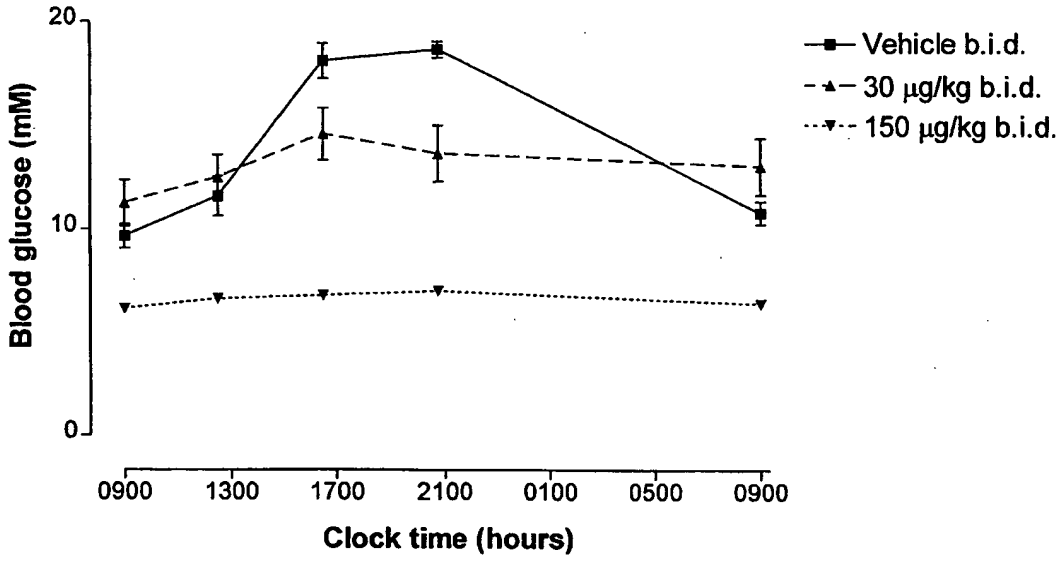
8. A method for increasing the insulin synthesis capability of a subject comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to said subject.

9. A method of delaying the progression of non-insulin requiring Type II diabetes to insulin requiring Type II diabetes comprising administering GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist to a subject suffering from Type II diabetes.

10. The method according to claim 7, 8 or 9 wherein the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is a GLP-1 derivative wherein at least one amino acid residue of the parent peptide has a lipophilic substituent attached.

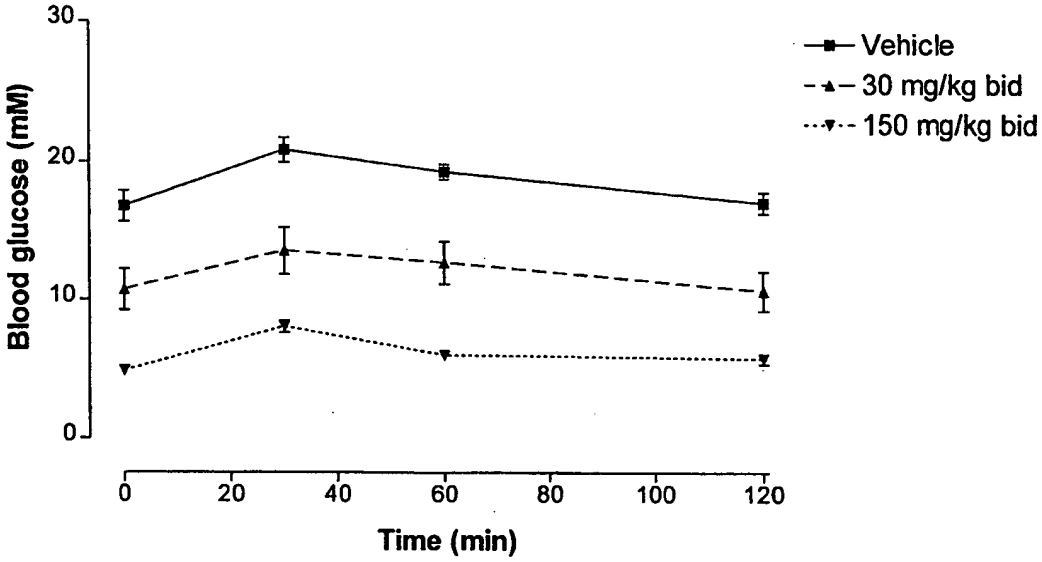
11. The method according to claim 10 wherein the GLP-1 derivative is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

12. The method according to claim 7, 8 or 9 wherein the GLP-1 or an analogue or a derivative thereof or a GLP-1 agonist is selected from GLP-1(7-37) and GLP-1(7-36) amide and the corresponding Thr^8, Met^8, Gly^8 and Val^8 analogues.



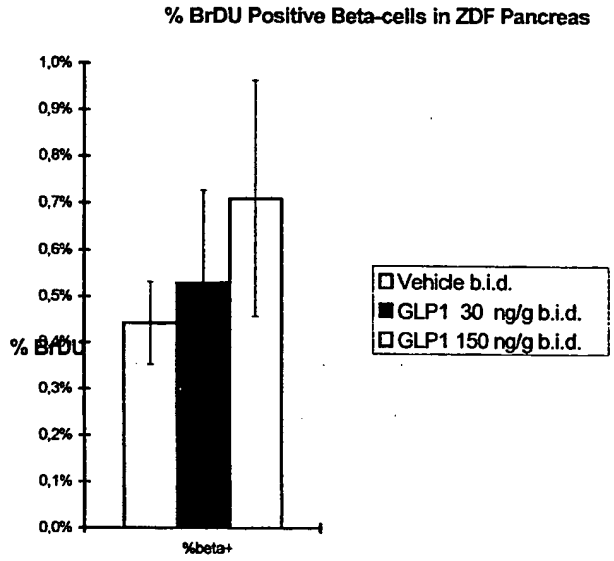
Twenty-four-hour profile of blood glucose (mean±SEM) in animals after 10 days of dosing.

Fig. 1



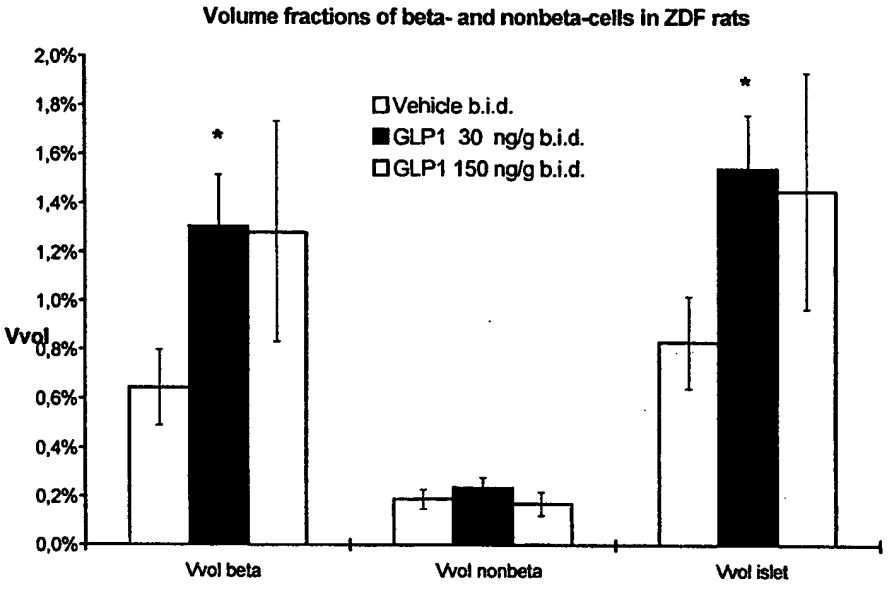
Blood glucose in animals after 36 days of dosing.

Fig. 2



Fraction of beta-cells in proliferation.

Fig. 3



Volume fractions of beta-cells, nonbeta-cells, and islets related to total pancreas volume.

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00424

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 38/26, A61P 3/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Diabetes, Volume 47, November 1998, Jens J. Holst et al, "Perspective in Diabetes. Inhibition of the Activity of Dipeptidyl-Peptidase IV as a Treatment for Type 2 Diabetes" page 1663 - page 1670	1-6
X	Diabetic Medicine, Volume 13, 1996, M.M. Byrne et al, "Human Studies with Glucagon-like-peptide-1: Potential of the Gut Hormone for Clinical Use" page 854 - page 860	1-6
X	WO 9808871 A1 (NOVO NORDISK A/S), 5 March 1998 (05.03.98)	1-6

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 1999	09 -12- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT DK/1999/00424

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 7-12
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT DK/1999/00424

Claims 7-12 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/09/99

International application No.
PCT/DK 99/00424

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9808871 A1	05/03/98	AU 3847897 A	19/03/98
		AU 4112497 A	19/03/98
		CZ 9900629 A	14/07/99
		EP 0929576 A	21/07/99
		NO 990950 A	28/04/99
		WO 9808872 A	05/03/98